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FDG at 7.8 MeV

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Abstract. I here report the fundamental performance of a new generation of compact medical cyclotrons for hospital-based PET tracer manufacture, exemplified with the FDG production numbers achieved by the first prototype of the GE GenTrace cyclotron. The proton energy is 7.8 MeV. After 3 years of extensive testing in a "physics lab" setting, which is door-to-door with our normal GMP production suite, I can now conclude that this cyclotron in conjunction with a standard GE Fastlab chemistry box easily achieves significant, reliable and compliant FDG output surpassing 15 GBq per batch at EOS, after 2 hours bombardment time. The details are reported below.

INTRODUCTION

The concepts of "point of demand", "bedside" or even "tabletop" cyclotrons for FDG production has been around for exactly 10 years now, since Ron Nutt boldly counteracted the "big is better" trend for regional FDG factories (ref.1). Still such small cyclotrons have not revolutionized the market, although anyone familiar with the logistics of supplying clinical PET scanners with tracers can see the beauty of the concept. During these ten years, many technical aspects of the idea have been furiously debated. To a much smaller degree, the ideas have been tested and proven in practice (ref.2). The underlying cyclotron technology (positive/negative ion, classical, AVF, superconductive cyclotrons) and the best energy have been discussed, as well as the necessary radiochemical and radiopharmaceutical support structure (synthesis cassettes, microfluidics, integrated QC). It is still fair to say, that the revolution in PET tracer supply can only happen when all the mentioned aspects of "FDG on demand" have been solved. In this paper I can report a very realistic and practical approach to FDG production using the standard GE Fastlab system coupled to my first prototype version of the new GE GENtrace 7.8 MeV cyclotron.

Material and Methods

GE has recently introduced to market a 7.8 MeV PET cyclotron (GENtrace) which is a high end bid for the ultra-small cyclotron. It is a conventional sector focused negative ion internal ion source cyclotron delivering 35-50 uA of protons to any of three targets mounted on a short external beamline. This allows for a compact but efficient shield centered on the target, with a less cumbersome shield around the cyclotron itself. The actual cyclotron used for this study is the number one prototype of the GENtrace. Although an early prototype, it is fully performance compatible with the final GENtrace, and has the same beam characteristics. Production of F-18 is completely automatic and requires only a few strokes of computer entry, before loading of target and bombardment starts. The target used is a shallow (2 mm) niobium cavity target with a gridded 12.5 um Havar® foil against the cyclotron vacuum. Beam is measured (ref.3) to be 7.8 +/-0.07 MeV with 85 % transmission of the grid.

The target (see figure 1) requires only 550 uL of O-18 water (HYOX, Rotem 97+%) inside the target chamber, but tubing and valve dead-volumes adds another 350 uL for at full cycle loading and irradiation. Target is pressurized with 20 bar argon (99.99%) during bombardment in the normal "open pressurized" mode. Transfer of irradiated water,

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flushing and drying is likewise done by argon through 1/16” PEEK tubing (0.25 mm i.d. below target and 0.75 mm i.d. above target). Target plumbing is otherwise very similar to the GE Minitrace configuration.

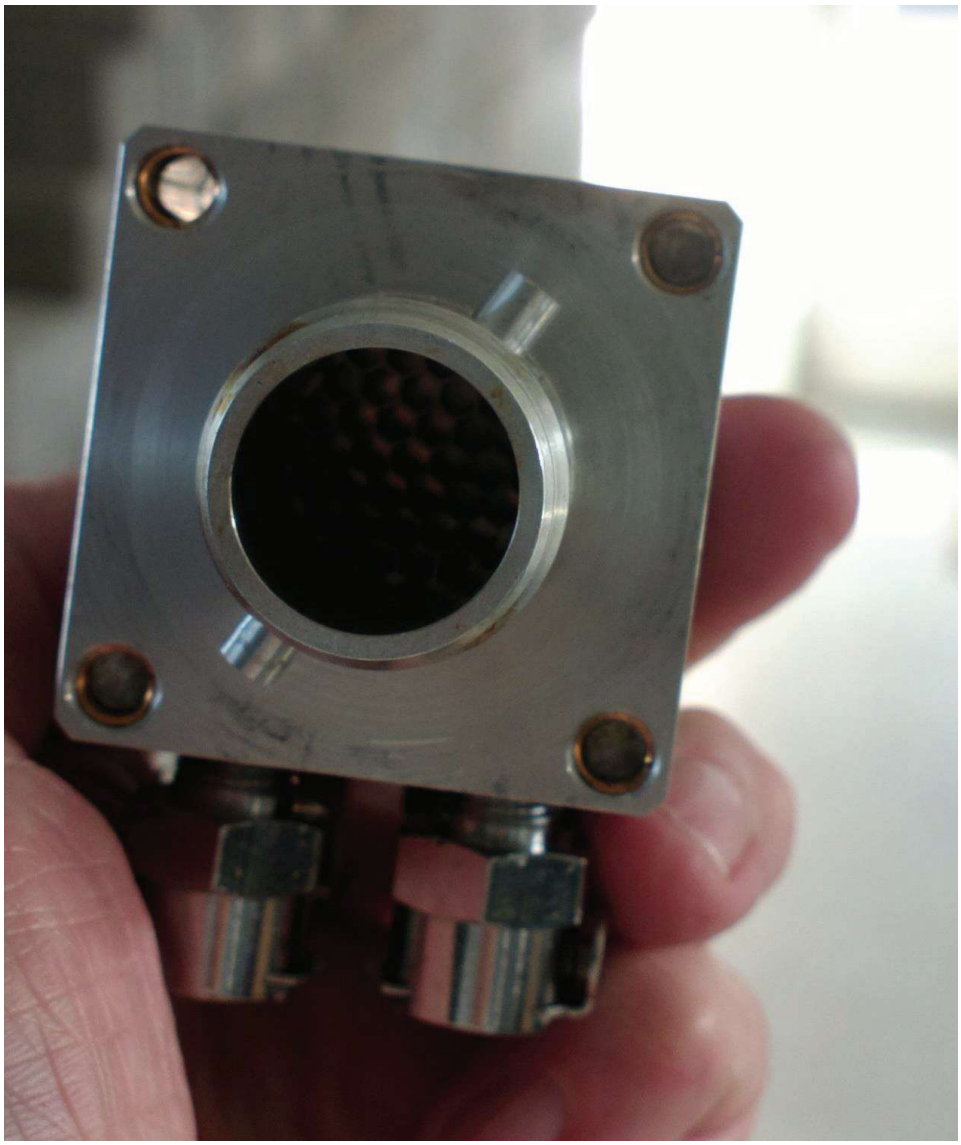

Figure 1- Prototype O-18 water target. Notice the grid.

Target and transfer lines are dried with argon at the end of a production day, but no other target or target line maintenance has been done during the 6 months of operation for the data taken in this study.

The reported bombardments were done completely automatic by the control system. It takes 7½ to 8 minutes from off-state to full and stable beam on target. A service mode exists within the control software, but the automatic production mode delivers as good or better stability than any human operator can do in service mode. Irradiations were done at 35 uA on target+ grid corresponding to 30uA into the target water. Beam currents and charge integration was initially checked by a Keithly2000 DVM, but no differences bigger than 3% could be detected between DVM measured and system reported values. Apart from the normal “bubbling noise” pressure variations (+/- 50 mbar RMS) with beam on, no change in target pressure was observed in any of the runs.

More than 85 F-18 production runs (60-120 mins) have been performed on the GENtrace prototype during the last two years, with some runs only aiming at establishing the F-18 EOB activity, production rate and specific activity of F-18 in the target water. Some of the early runs were also used to optimize the shielding of the target, as this early evaluation prototype was only intended for experimental bunker operation and arrived without shield. Shielding was experimentally optimized with movable blocks of normal concrete (2.3 g/cm3), normal polyethylene (0.91 g/cm3) and lead (11.3 g/cm3). Radiation levels on surface and at 100 cm distance from shield were measured with a calibrated RADDOS 200 survey meter (for the gamma level) and an ALNOR/Studsvik DIGIPIG 222A digital neutron survey meter. After initial target shielding optimizations, the residual radiation from the cyclotron itself could be measured and neutron yield from the cyclotron structure itself was minimized through graphite baffle placement and careful control of neutral beam loss.

F-18 activity in the target water was measured by emptying the target through 30 - 40 meter 1/16" Tefzel ® tubing into vials subsequently measured in a Veenstra VDC 505 XR dose calibrator. Observations were normally taken at two time points 10 minutes separated to exclude confounding by possible short lived isotopes. With highly enriched target water (>97 %) no short lived component was ever seen in the dose calibrator measurements.

Specific activity of F-18 in the freshly irradiated target water was measured in 15 runs by an adopted method, originally proposed back in 1975 by Noto et al (ref.4). It relies on a substoichiometric addition of aluminum chloride or lanthanum chloride in known (nanomole) amounts at slightly acidic conditions. After 15-30 minutes digestion at 60-80 deg. C, the mixture is assayed by paper TLC, thereby separating remaining free F-18 fluoride from reacted, cationic Al-F or La-F complexes. The method has been calibrated against titration of 100 fold dilute, presumably carrier free F-18 target water from high level PT-800 runs with known amounts of "cold" sodium fluoride. The method may be seen as rather generic and closely related to generally accepted methods for indirect detection of fluoride by ICPMS or ICPOES, and is also related to methods described in the patent in ref.5. This author suggests that the method may easily be simplified by use of a small cartridge QMA column to perform the quantitative separation of reacted and non-reacted F-18 fluoride for simple "equipment free" assays of F-18 specific activity.

For the full scale production of FDG, a further series of 12 dedicated runs (106-126 mins) were made at 35 uA on grid plus target, after which the irradiated water was transferred by 38 meter of 1/16"tefzel tubing to the activity inlet of an ordinary FASTLAB synthesizer. Transfer time (again) using argon was always below 1'45". Activity received in the Fastlab was taken from the FASTLAB report, using the built in solid state detector. No attempts could be made to directly measure the specific activity in these runs, but final product measurements of F-19 FDG consistently found levels below 0,05 mg/ml. This is consistent with the direct measurements of fluoride by the mentioned aluminium/lanthanum titration method. In 10 of the 12 runs, the target and transfer line were flushed by 1.2 ml ordinary O-16 water. This target flush water was included in the subsequent FDG synthesis, and appears to yield additional 5-8 % activity.

Three of the 12 FDG runs were performed on FDG citrate buffer cassettes and sequences, while the remainder was done on the phosphate buffer system. After synthesis, final activity, pH, radiochemical, radionuclidic and chemical purities were measured using the standard array of Ph Eur compliant analysis. No attempts were made at this instance to measure any microbiological parameters (sterility, endotoxins) as I regard these as being independent of the cyclotron platform under test.

Radionuclidic purity of the final FDG has been carefully studied using both HP(Ge) gamma spectroscopy (20- 27 hours EOS) and liquid scintillation counting.

FASTLAB synthesis time was 22 minutes, independent on choice of buffer system and sequence. The total turnaround time from start of cyclotron to EOS was less than 90 minutes (1 hour runs) or respectively 150 minutes (2 hour runs).

Results

F-18 yields

The yield of recovered F-18 activity in 85 experimental runs is given in table 1.

Table 1

Results of Activities out of target at EOB- current *) is grid+target. And **) is target only

Bombard minutes	I (μA)*	Activity EOB (GBq)	Activity steady state GBq	Activity per microAmp ** steady state GBq
30	35	10.3±0.8	60	2.0
60	35	19.2±2.2	61	2.0
120	35	28.5±3.0	54	1.8

The measured steady state yields/microamp (1.8-2.0) can be compared to the IAEA published recommended yields (ref.6). Allowing for 0.7 MeV energy loss in the foil and an approximate 20 % derating of IAEA yields going from O-18 gas to O-18 water, the official "theoretical" value of Ass/uA is 2.88 GBq. We thus routinely achieve 70 % of theoretical with little statistical variation. Of course, an EOB output of 29 GBq F-18 is not a typical "ultra-small" cyclotron figure, but allows for large batches of finished F-18 tracers even with longer synthesis time and low yields. The high F-18 production rate comes invariably with a corresponding shielding need: no F-18 nucleus can be made without an escaping neutron.

Neutron rate and shielding

From the steady state activity, it can be expected that the total neutron production rate in the F-18 target at 35 uA must be about 1E11 neutrons/second (including contribution from grid and foil). A similar number of high energy prompt gammas must also be produced. Various arrangements of concrete, concrete+plastic and concrete+lead were tested, but an optimal compact solution for target shield was found at (inwards to out):

100 mm lead	100 mm polyethylene and	750 mm concrete

.

This reduced the maximum dose rate on the concrete surface of the target shield to be less than 80 uSv/h at any point (equal neutron and gamma contribution, no forward peaking observed).

The present block structure is good for experiments (see figure 2), but not absolutely leak tight. Still, it is fascinating to be able to stand at reasonably close distance to the prototype and the target during operation, while radiation levels are still very moderate.

Integral shield on Product version

It is now demonstrated (at GE Medical Systems in Uppsala, Sweden) that the product version of this cyclotron (the GENtrace cyclotron) with its integral shield can achieve substantial further reduction in surface dose. No surface point on the product version integral shield exceeds 10 microSv/h). The product version (as realized at GE Medical systems in Uppsala, Sweden) is shown with shield in figure 3.

Figure 2 The prototype cyclotron photographed in operation – The right hand concrete bricks constitute the outermost layer of the target shield.

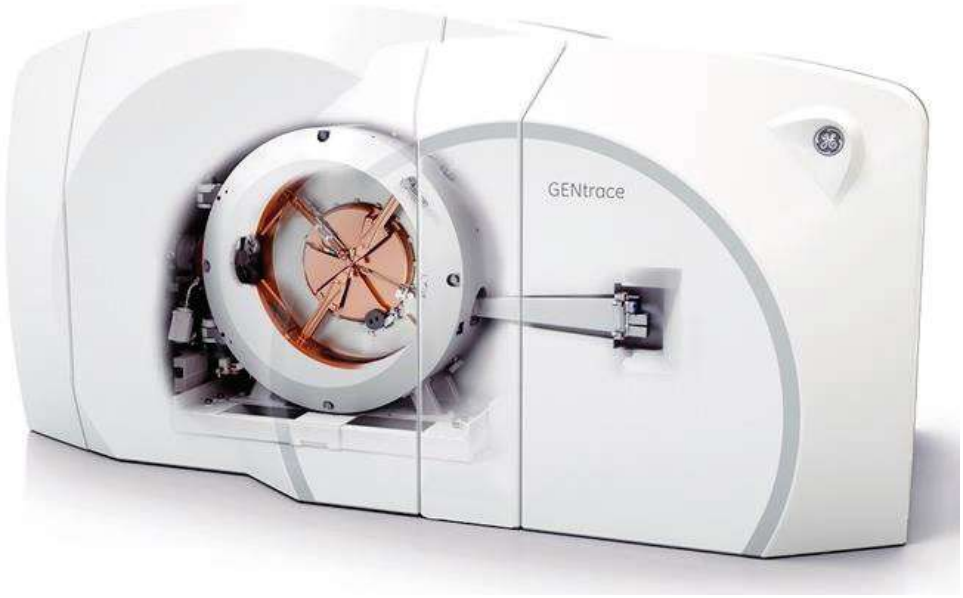

Figure 3- Cut-away rendering of the product version - GE GENtrace

The difference in appearance between figure 1 and 2 belies the close relationship. It is exactly the same magnet structure, and the two versions have the same beam characteristics (7.8 MeV, 35 microamp, 3 targets). However, the

turbopump has been moved up and to the lefhand side, allowing the whole machine to stand lower to the floor. At the same time, the beam line and targets have been moved up to a standard horizontal orientation.

Specific Activity of F-18

The titration method on target water showed consistently decreasing fluoride levels during the optimization runs, starting at about 600 nmol F in the target volume, but decreasing to 123±19 nmol in the latest series of 1- and 2 hour runs. This corresponds to a specific activity of about 300 GBq/umol (8Ci/umol) in the target water. No clear connection was seen between length of irradiation and fluoride contents.

FDG yields

The 12 dedicated FDG production runs on FASTLAB gave decay corrected FDG yields of 78±9% (67 % non-corrected). No significant difference was seen between phosphate and citrate systems and bombardment time had no influence on the relative yield either. Resulting FDG batch activity after 1 hour runs was 11-14 GBq, and for 2 hour runs 15-21 GBq.

FDG quality control

As could be expected all the normal QC parameters were completely as usual for FASTLAB FDG, with pH 5.2-7.0 and Radiochemical Purity 98.7 – 99.4%. Residul contents of the organic solvent MeCN was 12-25 ppm. All batches would have been compliant with requirements for FDG in Ph.Eur. monograph and our own FDG specifications.

The radionuclidic purity was given special attention as this could be a possible influence of the change in cyclotron and beam energy. However, despite that kBq levels of Co-56 could be found on each of the QMA columns (as usual), no gamma emitting radionuclides other than F-18 was found in the final product. Tritium was, as expected , found in the used target water at a level of about 50 kBq/ml, which is of course significantly lower than for standard PETtrace target water. No tritium was found in the final FDG product (MDA =23 Bq/ml, n=3).

Conclusion

The GENtrace cyclotron prototype convincingly demonstrates the capability to produce significant amounts of useful and compliant FDG in short time and with a small footprint. Getting 15 GBq of FDG at EOS just 90 minutes after cold system startup, and then easily 15 GBq more every second hour is enough to support ANY clinical FDG operation, no matter how many scanners on site. Some regional distribution is even possible with this production rate. It demonstrates that 7.8 MeV proton energy is indeed more than enough for F-18, and this gives the GENtrace an important surplus capacity in a small PET site operation. This capacity may well be used for C-11 or Ga-68,…. but that is a totally different story.

ACKNOWLEDGMENTS

This long-term study and development phase has only been possible at my university based research laboratory thanks to the qualified, resourceful and respectful, arm's length collaboration with GE Medical Systems, Uppsala, Sweden. They have provided this first prototype cyclotron to my lab "as is", openly stating the prototype status and uncompleted software and support system. This actual copy of the machine is installed as a research platform for general development of isotope production at very low energy cyclotrons and is not intended for clinical supply.

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